Election/Restrictions:

The Examiner stated that the applicant's election with traverse of group III in Paper No. 10 is acknowledged. The Examiner stated that the traversal is on the ground(s) that the restriction is improper and illegal. The Examiner alleged that this is not found persuasive because the invention of groups I, II, and IV are drawn to separate and distinct inventions that all have unique outcomes, purposes and methodological steps that require a distinct search of the prior art. The Examiner alleged that the inventions of group I, II, and IV are classified in distinct classes and subclasses, therefore warranting the separation of the invention. The Examiner stated that the requirement is still deemed proper and is therefore made **FINAL**.

Information Disclosure Statement:

The Examiner stated that the information disclosure statement filed 8/31/2001 fails to comply with 37 CFR 1.98 (a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The Examiner stated that it has been placed in the application file, but the information referred to therein has not been considered.

In response, applicants respectfully direct the Examiner's attention to the following documents allegedly not received by the patent office as part of the information disclosure statement filed on August 31, 2001, i.e. below listed references , attached hereto

as **Exhibits 1-5**. To ensure consideration of all references listed on Form PTO-1449 attached hereto as **Exhibit B**, applicants list below all 13 references. Please note that copies of below listed references 1 and 7-13 were provided in the information disclosure statement filed on August 9, 2001. Applicants respectfully request that all below listed references, i.e. 1-13, now be considered by the patent office.

1. WO98/22138 A1 (The Trustees Of Columbia University In The City Of New York) 28 May 1998;

2. Hori et al. 'The Receptor for Advanced Gycation Endproducts: Implications for the Development of Diabetic Vascular Disease. Fundam. Clin. Cardiol.' In: The Endothelium in Clinical Practice. January 1997, Chapter 11, pages 311-329 **(Exhibit 1)**;

3. Yan et al. Amyloid-beta Peptide-Receptor for Advanced Glycation Endproduct Interaction Elicits Neuronal Expression of Macrophage-Colony Stimulating Factor: A Proinflammatory Pathway in Alzheimer Disease. Proc. Natl. Acad. Sci. 13 May 1997, Vol. 94, No. 10, pages 5296-5301 **(Exhibit 2)**;

4. Schmidt et al. V-domain of Receptor for Advanced Glycation Endproducts (RAGE) Mediates Binding of AGEs: A Novel Target for Therapy of Diabetic Complications. Circulation. 21 October 1997, Vol. 96, No. 8 Suppl., page I37 **(Exhibit 3)**;

5. Hori et al. The Receptor for Advanced Glycation Endproducts (RAGE) Is A Cell Surface Receptor for Amphoterin in the Developing Central Nervous System (CNS) to Promote Neurite Outgrowth. FASEB J. 1995, Vol. 9, No. 3, page A382 **(Exhibit 4)**;

6. International Search Report of International Application No. PCT/US99/08427, dated August 19, 1999 **(Exhibit 5)**;

7. Morser et al., U.S. Patent No. 5,864,018, filing date April 16, 1996;

8. Morser et al. PCT International Application No. PCT/EP97/01832, filed 11 April 1997, published October 23, 1997, Publication No. WO 97/39121, Advanced Glycation Endproduct Receptor Peptides and Uses Thereof;

9. Morser et al. PCT International Application No. PCT/EP97/01834, filed April 11, 1997, published October 23, 1997; Publication No. WO 97/39125, Antibodies Against the Advanced Glycation Endproduct Receptor and Uses Thereof;

10. Park, L., et al. (1998) "Suppression of accelerated diabetic atherosclerosis by soluble Receptor for AGE (sRAGE)" Nature Medicine, 4:1025-1031;

11. Vlassara, H., et al. (1995) "Identification of Galectin-2 as a high affinity binding protein for Advanced Glycation Endproducts (AGE): a new member of the AGE-Receptor complex" Molecular Medicine, 1:634-646;

12. Vlassara et al., US Patent 5,585,344;

13. Yan S-D, Chen X, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Morser J, Migheli A, Nawroth P, Stern DM, Schmidt A-M: RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996;382:685-691.

Claim Rejections Under 35 USC §112, second paragraph:

The Examiner rejected claims 74-75 under 35 U.S.C 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that while the applicant may be his or her own lexicographer, a term in a claim may be given a meaning repugnant to the usual meaning of that term. The Examiner stated that see *In re Hill*, 161 F.2d 367,73 USPQ 482 (CCPA 1947). The Examiner alleged that the terms "*cadherin*" and "*intergrin*" in claim 74 and 75 are used by the claims to mean "*extracellular matrix molecule*" while the accepted definitions of the terms are receptors. The Examiner stated that it is also noted that claim 74 is an improper Markush group that have species that are not related to the genus of extracellular matrix molecules.

In response, without conceding the correctness of the Examiner's position, but to expedite prosecution of the subject application, applicants have hereinabove canceled claims 74-75 without prejudice or disclaimer to applicants' right to pursue the subject matter of this claim in a later-filled application. Therefore, applicants contend that canceled claims 74-75 obviate the Examiner's above rejection. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this objection.

Claim rejections under 35 U.S.C. §112, first paragraph:

Claims 57-78:

The Examiner rejected claims 57-78 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a soluble RAGE molecules as an agent which inhibits tumor invasion, does not reasonably provide enablement for agents in general or any agent other than soluble RAGE. The Examiner alleged that the specification does not enable any person skilled in the invention commensurate in scope with these claims. The Examiner alleged that claims 57-78 are drawn to a method of identifying agents that inhibit tumor invasion by admixing tumor cells with an agent, wherein a decrease in spreading indicates an agent that is able to inhibit invasion of tumor cells. The Examiner stated that although the claims are enabled for the use of a soluble form of RAGE as an agent to inhibit invasion of a tumor cells, the instant specification has not enabled the use of other agents (polypeptides, peptidomimetics, nucleic acids, carbohydrates, lipid, antibody or fragments, or small molecules). The Examiner

alleged that because the breadth of the claims encompass agents that are not described in the specification in such a way that would allow one of skill in the art to practice the claimed invention, the instant specification invites of skill in the art to experiment. The Examiner stated that the factors which must be considered in determining undue experimentation are set forth in *In re Wands* 8 USPQ2d 1400. The factors include: (1) quantity of experimentation, (2) the amount of guidance presented, (3) the presences or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the predictability of the art and, (7) breadth of the claims.

The Examiner alleged that with regards to factors one and two cited above, the quantity of experimentation needed to determine which agents are able to inhibit invasion of tumor cells and the amount of decrease in cellular spreading which is needed to indicate that an agent is a potential candidate for inhibiting tumor invasion, is high because the instant specification has not adequately disclosed specific methodological steps, for each agent intended to be identified, which must be followed in order to reach the desired end point.

The Examiner alleged that with regards to factors four, five, and six cited above, it is noted there is a great deal of unpredictability associated with the identification of agents/drugs that are effective for the treatment or prevention of cancer. As evidence by Gura *et al.* methods for identifying potential new

cancer drugs can at times be difficult and ineffective (Science 1997 Nov 7 ; 278:1041-1042). The Examiner stated that the instant fails to provide a specific methodological procedure for identification of such agents, specifically, the agents mentioned in the instant application. The Examiner stated that for example, one of ordinary skill would be forced into undue experimentation to begin to look for peptides and analogs, peptidomimetics, inorganic and organic compounds, antibody or fragments thereof, and small molecules, because one of ordinary skill would find it difficult to even begin to search the countless number of potential candidates that could be used to obtain the desired end point.

The Examiner alleged that with regards to factors, three and seven cited above, it is noted that the instant specification provides examples of how to use one particular agent, namely soluble RAGE, but does not provide examples or evidence that other agents can be identified and what it is that is that one of skill in the art is to look for in the identification of agents which inhibit invasion of tumors. The Examiner stated that the breadth of the claims encompass the identification of any agent that is able to inhibit invasion, while the specification has only enabled the use and identification of a soluble form of RAGE. The Examiner stated that it is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves, see *In re Gardner et al.* 166 USPQ 138 (CCPA 1970).

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the presently claimed invention, i.e. a method for identifying an agent which prevents tumor invasion in a local cellular environment by inhibiting RAGE amphoterin interaction, is enabled.

The Examiner recites that the specification "while enabling for a soluble RAGE molecule as an agent which inhibits tumor invasion, does not reasonably provide enablement for agents in general or any agent other than soluble RAGE." See page 3, paper #11. In addition, the Examiner recites that "the instant specification fails to provide a specific methodological procedure for the identification of such agents" See page 5, paper #11.

In response to the Examiner's recitation that "the instant specification fails to provide a specific methodological procedure for the identification of such agents". Contrary to the Examiner's above assertion, applicants contend that the claims of the present invention are directed to a step-wise method for identifying an agent which inhibits tumor invasion in a local cellular environment. Applicants respectfully direct the Examiner's attention to claim 57 which recites as follows:

" A **method for identifying an agent** which inhibits tumor invasion in a local cellular environment **which comprises**:

(a) providing a solid support coated with amphoterin;

(b) contacting the solid support with a tumor cell which expresses receptor for advanced glycation endproducts (RAGE) under appropriate cell culture conditions for cell migration and growth;

(c) admixing to the tumor cell culture of step (b) an agent to be tested;

(d) determining the amount of spreading of the tumor cells on the solid support, and

(e) comparing the amount of spreading of the tumor cells determined in step (d) with the amount of spreading determined in an identical tumor cell culture in the absence of the agent, **wherein a decrease in the amount of spreading determined in step (d) indicates that the agent is identified as an agent which inhibits tumor invasion** in the local cellular environment" [emphasis added].

Therefore, applicants contend that the claims of the present invention are directed to a specific method for identifying an agent which inhibits tumor invasion in a local cellular environment and the present invention is enabled.

In response to the Examiner's recitation that "the specification while enabling for a soluble RAGE molecule as an agent which inhibits tumor invasion, does not reasonably provide enablement for agents in general or any agent other than soluble RAGE."

Applicants respectfully direct the Examiner to the MPEP §2164.01(b) which recites as follows:

> "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied"

The specification recites the effect of administration of sRAGE on numbers of lung surface metastases in figure 8A. Specifically, the mean tumor volume of sRAGE treated mice (20μg/day) was decreased 2-fold compared to the in MSA-treated control mice. See page 25, lines 25-34, and Figure 8A. Further, the specification recites that "soluble RAGE (sRAGE) may thus represent a model structure for the development of agents to limit tumor growth and invasion into the local environment, and, potentially, the development of distant metastases." See page 22, lines 24-28. Therefore, the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, i.e. a method for identifying an agent which prevents tumor invasion in a local cellular environment by inhibiting RAGE/amphoterin interaction, and the presently claimed invention is enabled.

Applicants contend that these comments obviate the Examiner's above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 57 and 61:

The Examiner rejected claims 57 and 61 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The Examiner alleged that the steps or protocol needed to identify agents that are nucleic acids using the steps of claim 57 are critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. The Examiner stated to see *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The Examiner stated that the instant application claims to identify agents that are able to inhibit invasion of tumor cells. The Examiner stated that an agent named in claim 61 fails to be used in the steps outlines in claim 57, wherein the steps seem to be referring to methodological steps for the identification of protein based or chemical agents, and not for nucleic acid molecules. The Examiner stated that the instant application is silent in this regard, because the specification has not disclosed how a protein based assay for the identification of agents can be used as a method for the identification of agents can be used as a method for the identification of nucleic acid agents.

In response, without conceding the correctness of the Examiner's position but to expedite the examination of the present application, applicants have hereinabove canceled claim 61 without prejudice or disclaimer to applicants' right to pursue the subject matter of this claim in another application. Accordingly, the claims no longer recite the alleged limitation "a nucleic acid". Applicants contend that this comment obviates the Examiner's above

rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 57-61, 66, 71-72, 76-78 under 35 U.S.C. 103(a) as being unpatentable over Hori *et al.* (J. Biol. Chem. 1995; 270(43):25752-25761) in view of Miki S *et al.* (Biochem Biophys Res Commun 1993 Oct 29;196(2):984-9). The Examiner alleged that claims 57-61, 66, 71-72, 76-78 are drawn to a method of identifying an agent, wherein the agent is soluble RAGE, that is able to inhibit invasion of tumor cells. The Examiner stated that this application currently names joint inventors. The Examiner stated that in considering patent ability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. The Examiner stated that the applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103 (a). The Examiner stated that the factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The Examiner alleged that Hori *et al.* disclose a method of inhibiting the binding of amphoterin to RAGE by incubating an agent, sRAGE or soluble RAGE, to plates coated with amphoterin. The Examiner alleged that Hori *et al.* used this method to identify the amount of cell growth was inhibited by sRAGE. The Examiner alleged that Hori *et al.* further disclose of the involvement of amphoterin interaction with RAGE and that an important mechanism for the invasiveness of neoplastic lesions is dependent on the interaction of amphoterin with RAGE (pg 25760 column 2). The Examiner stated that Hori *et al.* however do not disclose of tumor association with RAGE. The Examiner alleged that Miki *et al.* do disclose of RAGE expression in cancer cells, and further disclose that RAGE is associated with cellular growth. The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to develop a method of identifying an agent, namely a soluble RAGE, that was able inhibit cellular invasion, because the prior art provides sufficient motivation to practice the invention as claimed. The Examiner alleged that the suggestion or motivation for doing what the applicant has claimed is that it was already known that sRAGE was available and that it was able to inhibit cellular growth (Hori et

al.). The Examiner alleged that it was also known that RAGE and amphoterin may have been an important interaction in neoplastic events (Hori et al.). The Examiner alleged that it was also known that cancerous cells express RAGE (Miki et al.) and that since cancerous cells express such receptors, an agent that is able to inhibit normal cell growth may indeed be able to inhibit cancerous cells from growing/spreading and hence invading. The Examiner alleged that it would have been prima facie obvious at the time of the invention to discern of a method to identify agents that are able to inhibit invasion of tumor cells using amphoterin and sRAGE.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the cited references, namely Hori et al. in view of Miki et al. do not render obvious the claimed invention.

Initially, applicants point out that claim 57 recites as follows:

> " A method for identifying **an agent which inhibits tumor invasion** in a local cellular environment which comprises:
>
> (a) providing a solid support coated with amphoterin;
>
> (b) contacting the solid support with **a tumor cell** which expresses receptor for advanced glycation endproducts (RAGE) under appropriate cell culture conditions for cell migration and growth;

(c) admixing to the tumor cell culture of step (b) an agent to be tested;

(d) determining the amount of spreading of the tumor cells on the solid support, and

(e) comparing the amount of spreading of the tumor cells determined in step (d) with the amount of spreading determined in an identical tumor cell culture in the absence of the agent, wherein a decrease in the amount of spreading determined in step (d) indicates that the agent is identified as **an agent which inhibits tumor invasion in the local cellular environment**" [emphasis added].

Hori et al. does not teach or suggest any relationship between RAGE and tumors, much less a method for determining whether an agent inhibits tumor invasion in a local cellular environment. The Examiner concedes this fact and recites as follows: "Hori et al. however do not disclose of tumor association with RAGE" See paper 11, page 7, second paragraph. Therefore, there is no motivation in Hori et al. to derive the presently claimed invention, i.e. a method for identifying an agent which inhibits tumor invasion in a local cellular environment by inhibiting RAGE/amphoterin binding.

To compensate for the lack of any disclosure of a relationship between RAGE and tumors in Hori et al., the Examiner relies on Miki

et al. which recites the presence of RAGE on RCC cells. Applicants contend that Miki et al. does not provide any objective teaching of what is missing from Hori et al., i.e. that the mere expression of RAGE and its alleged role in the growth of RCC cells renders obvious a role for RAGE/ligand binding in tumor invasion and metastasis. Applicants respectfully point out that given the complexity of tumor cell biology, absent the applicants experimental data, one of skill in the art at the time of the present invention would not have been able to reasonably determine the role of RAGE in tumor cell invasion. Therefore, the Examiner's combination of Hori et al. and Miki et al. simply take the applicants disclosure and substantial experimental data regarding the invasive potential of C6 glial cells as a blueprint for piecing together the above-identified prior art to defeat patentability.

In support, the specification recites that "a number of factors have been suggested to be important in the ability of tumors to grow and invade their local environment." See page 26, lines 35-37. Further identifying the complex nature of tumorogenesis, the specification recites that "certainly, a **multitude of factors** have been postulated to result in local tumor growth and invasion"[emphasis added]. See page 27, lines 11-12. In addition, the specification recites that "while **precise mechanisms** underlying the beneficial effects of sRAGE are under study in this model of local tumor growth, our data suggest that sRAGE may represent a **novel structure** in the design of agents to limit tumor spread and invasion"[emphasis added]. See page 27, lines 35-38 and page 28,

line 1.

The applicants contend that the cited references, namely Hori et al. in view of Miki et al. do not demonstrate the role of RAGE in tumor cell invasion as disclosed in the present invention and therefore do not render obvious the claimed invention. Accordingly, applicants contend that these comments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims .

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other than the $460.00 for a three-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

11/7/02
John P. White Date
Reg. No. 28,678

Exhibit A

--76. (Amended) The method of claim [61]57, wherein the agent inhibits binding of RAGE to amphoterin.--

--77. (Amended) The method of claim [61]57, wherein the agent binds to RAGE.--

--78. (Amended) The method of claim [61]57, wherein the agent binds to amphoterin.--